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EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,280	URATA ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-53* is/are rejected.

7)☒ Claim(s) *48-50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) ~~Paper No~~(s)/Mail Date 10/13/04, 10/26/04, 12/13/04 & 4/13/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-53 ARE PRESENTED FOR EXAMINATION

Applicants' Preliminary Amendment filed October 13, 2004 and Information Disclosure Statements filed April 12, 2004, October 13, 2004, October 26, 2004 and December 13, 2004 have been received and entered into the application.

Accordingly, the specification at page 1, paragraph [0001] and page 5, paragraph [0021] have been amended. Also, as reflected by the attached, completed copies of forms PTO/SB/08A/B and 1449A/B/PTO, (7 sheets), the Examiner has considered the cited references.

Claim Objection

Claims 48-50 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The claims are directed to method limitations, i.e., "the administration to the patient occurs...", while the claim from which they depend defines something that is static, i.e., a kit, and does not include something which is dynamic.

Applicants are required to either (i) cancel the claims or (ii) amend the claims to place them in proper dependent form in response to this Office action.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the treatment of a cardiovascular disorder, such as atherosclerosis or hyperlipidemia, does not reasonably provide enablement for the prophylaxis of

the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Overcoming this Rejection

In order to overcome the present rejection, Applicants may wish to consider amending the claims by deleting the term "prophylaxis".

Statement of Rejection

In regard to the prophylaxis of the above conditions, the term "prophylaxis" has been interpreted in a broad, reasonable manner to indicate that the cardiovascular conditions may be kept from *ever* occurring in a patient, (see MPEP § 2111.01 regarding the basis of the broad/reasonable standard employed by the Examiner).

Further, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the state of the art and predictability or unpredictability thereof;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation. The Examiner has noted the diseases included in the claims that Applicants have indicated as being capable of being prevented through the practice of the claimed method. For the purposes of consideration under 35 U.S.C. § 112, first paragraph, the Examiner has focused on the specific disorder of atherosclerosis and/or hypercholesterolemia. However, the reasons stated here concerning the burden of enabling the prevention of atherosclerosis/hyperlipidemia apply also to the other related diseases, i.e., coronary heart disease, coronary artery disease and hypoalphalipoproteinemia.

Factors 1 and 2) The claimed invention is directed to a method of for the treatment or prophylaxis of cardiovascular disorders in a patient comprising administering the claimed compound, i.e., S-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl]-2-methylpropanethioate, (hereinafter "Compound 1" or "JTT-705", see the Okamoto et al. *Nature* reference cited by the Examiner with regard to the latter designation) in a pharmaceutical composition with food.

Factor 3) There is a known unpredictability in the art when engaging in the therapy of patients known to have a cardiovascular condition such as atherosclerosis or hypercholesterolemia. Factors that predispose a patient to these condition are known in the art and are acknowledged by *The Merck Manual* (cited by the Examiner; see page 387, section under the heading "Risk Factors"). Some of these factors include hypertension, elevated serum lipids, specifically cholesterol and triglycerides, cigarette smoking, diabetes mellitus and obesity. However, the presence of any one or more of these factors does not necessarily guarantee the

development of this disorder. There are a number of efficacious therapies, such as statins, directed towards the treatment of patients with atherosclerosis and/or hyperlipidemia and the use of any one or more of these therapies has demonstrated efficacy in reducing the severity of the disorders within a medically acceptable range or attenuates the factors, e.g., elevated lipid/cholesterol levels closer to a medically acceptable range (see, for example in Jones et al., the abstract "Comparative Dose Efficacy Study of Atorvastatin versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia (The CURVES Study"; 1998, cited by Examiner) in patients with these conditions. However, there is a high degree of unpredictability in determining therapies that can be used in the prevention, i.e., prophylaxis, of hypercholesterolemia and/or atherosclerosis because the etiology and/or pathophysiological manifestations associated with these conditions are generally complex and are not particularly well understood.

Factor 4) Applicants have merely disclosed, i.e., have not objectively demonstrated, that the claimed method results in the prophylaxis of a cardiovascular disorder, such as atherosclerosis and/or hypercholesterolemia, or any of the other disorders recited in the present claims. Based on the discussion in Section 3 above, however, such disclosure clearly is not adequate direction or guidance as to how the claimed active can be employed to actually accomplish the prevention of the claimed cardiovascular conditions, such as atherosclerosis or hypercholesterolemia, in a predictable manner.

Factor 5) The specification is devoid of any data showing the effect of the claimed composition against any cardiovascular disease. Pages 12-18 of the specification, as well as Figures 1-5, describe and show the effect of food on the pharmacokinetics of Compound 1 as

well as the effects on cholesteryl ester transfer protein, ("CETP") by the ingestion of both food and Compound 1.

Further, as set forth in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contain therein which must be relied on for enabling support*; assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling." (emphasis added).

Here, the objective truth of the statement that a cardiovascular diseases, such as hyperlipidemia and/or atherosclerosis could be prevented is doubted because the *Harrison's Principles of Internal Medicine* (cited by the Examiner) teaches "Thus *prevention of atherosclerosis, rather than treatment is the goal.* Although an effective program has not been established with certainty, enough is known to act as a guide both in identification of those with a higher risk and in development of conservative measures that probably will *reduce* that risk. Thus, prevention currently is equated with risk factor reduction." (emphasis added and original), (page 1116, col. 1, second paragraph under the heading "Prevention"). Accordingly, it appears that at best, only the reduction of the risk of developing atherosclerosis is possible and such is not what has been disclosed or enabled by the present application which recites prophylaxis.

Factor 6) The burden of enabling the prevention of a disease state, such as atherosclerosis or hypercholesterolemia, or any one of the selection of cardiovascular diseases recited in the present claims, is much greater than that of enabling the mere treatment of these diseases. Because the present specification would not enable the skilled artisan to prevent atherosclerosis, or any of the other specified cardiovascular conditions, a clear burden of undue experimentation

would be placed upon the skilled artisan in order to practice this aspect of the invention who would not be imbued with at least a reasonable expectation that such would be possible from the artisan's knowledge taken with Applicants' application papers.

Factor 7) Conventional therapies, such as statins (also known as HMG-CoA reductase inhibitors, see abstract of Jones et al., cited by the Examiner), used to treat hyperlipidemia, were well known in the art as an efficacious treatment for hypercholesterolemia, which was known to be associated with coronary artery disease (page 582, col. 1, first paragraph under the abstract). The use of these conventional therapies in treating a specific patient population, that is, those patients known to be experiencing hypercholesterolemias, was well defined in the art and allows for predominantly predictable and invariable results, in that it was well known that this type of therapy would reduce the incidence of morbidity or mortality associated with atherosclerosis and reduce the risk of recurrence of these symptoms, (note *Harrison's* at page 1111, col. 2, under the heading "Management of Hyperlipidemias"). However, it is established above in Section 3 that it is more difficult to prevent the occurrence of the disease than it is to attenuate the manifestations of this disease since it cannot be guaranteed that any patient exhibiting one or more of the factors recognized to predispose a patient to this condition will develop said condition.

Furthermore, the burden of enabling the prevention of or delaying the progression of **any** of the cardiovascular diseases or disorders recited in the present claims would be much greater than that of enabling the treatment of such diseases. In the instant case, the specification does not provide guidance as to how one skilled in the art would accomplish the objective of prevention or delaying the progression of such diseases or how a patient could be kept from ever

developing these diseases. The artisan would require a disclosure, including significant data, above the mere, objective teaching of prophylaxis in order to accept that such could actually be accomplished.. Also, the present specification does not provide any guidance as to a specific protocol to be utilized in order to show the efficacy of the presently claimed active ingredients for the prevention of such a cardiovascular disease.

Additionally, it is highly unlikely, and the Office would require substantial and convincing evidence to support the contention that the Compound I, or active forms thereof could actually prevent the development of the claimed cardiovascular diseases by simply administering, by any method, an amount of the claim specified active agents. The specification fails to enable one of ordinary skill in the art to practice the presently claimed method for preventing the development of such diseases.

The term "prophylaxis" or "preventing" is synonymous with the term "curing" (as per the reasonable and broad standard as set forth in the MPEP at § 2111) and both circumscribe methods of treatment having absolute success. Because absolute success is not reasonably possible with a vast majority of diseases/disorders, especially those having etiologies and pathophysiological manifestations that are as complex and/or poorly understood as the diseases or disorders recited in the present claims, (see, for example, *Harrison's* beginning at page 1108, col. 2, under the heading "Theories of Atherogenesis"), the specification is viewed as lacking an adequate written description of how any of the above-mentioned diseases may be actually prevented.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in

the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that prevention of hypercholesterolemia and/or atherosclerosis or any one of the selection of diseases or disorders recited in the present claims could be achieved. In order to actually achieve the prevention of any of these conditions, it is clear from the discussion above that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize, and Applicant has failed to demonstrate that atherosclerosis, hypercholesterolemia or any one of the selection of diseases or disorders recited in the present claims could actually be prevented, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this embodiment of the claimed invention. Accordingly, claims 34-43 are deemed properly rejected.

Legal Standard for Anticipation/Inherency Under - 35 USC § 102

To anticipate a claim under 35 U.S.C. § 102, a single prior art reference must place the invention in the public's possession by disclosing each and every element of the claimed invention in a manner sufficient to enable one skilled in the art to practice the invention. *Scripps Clinic & Research Foundation v. Genetech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q.2d 1001, 1001 (Fed. Cir. 1991); *In re Donahue,* 766 F2d531, 533, 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). To anticipate, the prior art must either expressly or inherently disclose every limitation of the claimed invention. *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303, 1303 (Fed. Cir. 1999) (citing to *In re Schreiber,* 128 F.3d 1473, 1477, 44

U.S.P.Q. 1429, 1431 (Fed. Cir. 1997)); *Atlas Powder Co. v. Ireco Inc.,* 190 F.3d 1342, 1347, 51 U.S.P.Q.2d 1943, 1946 (Fed. Cir. 1999). To inherently anticipate, the prior art must necessarily function in accordance with, or include, the claimed limitations. *MEHL/Biophile*, 192 F.3d at 1365, 52 U.S.P.Q.2d at 1303. However, it is not required that those of ordinary skill in the art recognize the inherent characteristics or the function of the prior art. *Id.* Specifically, discovery of the mechanism underlying a known process does not make it patentable. See also MPEP §§ 2112, 2112.02 and 2145(II).

Multiple Reference 35 U.S.C. § 102 Rejections

This Office action contains at least one rejection under 35 U.S.C. § 102 based on multiple references. The additional references is relied on to explain the meaning of a term used in the primary reference or to show that a characteristic not disclosed in the primary reference is inherent. Accordingly, the Examiner's reliance on multiple references is proper. "Normally, only one reference should be used in making a rejection under 35 U.S.C. § 102. However, a 35 U.S.C. § 102 rejection over multiple references has been held to be proper when the extra references are cited to:

(A) Prove the primary reference contains an "enabled disclosure;"

(B) Explain the meaning of a term used in the primary reference; or

(C) Show that a characteristic not disclosed in the reference is inherent." (See MPEP § 2131.01).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

I Claims 1-6, 10, 16-21, 25-30 and 34-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Okamoto et al., (the *Nature* reference, cited by the Examiner).

Okamoto et al. teach the administration of JTT-705, i.e., the claimed compound, (see page 204, Table 1, last listed compound) *in the diet* (page 205, col. 1, first sentence of the first full paragraph) of rabbits, i.e., broadly interpreted as a patient as presently claimed, fed a 0.2% cholesterol diet and the effects of such compound, which was contained in the diet, i.e., food, of the rabbits, on plasma CETP activity, plasma lipids, serum HDL, subfractions, serum apoA-1 and aortic atheroma (see Table 2, page 205; compare to present claims 1, 4, 5, 19, 20, 25, 28, 29, 34, 35, 38 and 39).

The authors report that "the thioester JTT-705 produced 95% inhibition of CETP activity at an oral dose of $30mgkg^{-1}$ in Japanese white rabbits", (see page 204, col. 1, first full paragraph above Table 1, lines 3-4). At the 4^{th} column in Table 2 on page 205, the average body weights of the rabbits are reported for all groups of rabbits in the study, including those receiving JTT-705. Such weights are listed in kilograms and in terms of months into the study and are 2.41 ± 0.04 at 0 months, 2.92 ± 0.07 at 3 months and 3.23 ± 0.07 at 6 months. Multiplying the rate of drug administration by the weight, the amounts administered the rabbits correspond to 72.3 ± 1.2 mg,

87.6 ± 2.1 mg and 96.9 ± 2.1 mg. which amount are not patentably distinct from "about" 100 mg or 300 mg, i.e., the lower limits of present claims 2, 3, 17, 18, 26, 27, 36 and 37.

While the authors do not report the pharmacokinetic results after such administration, such would have been inherent to the prior art method which otherwise meets the presently claimed requirements for the drug, amounts, the host and the physiological environment in which the administered drug would exist.

Respecting claims 6, 21, 30 and 40, the requirement therein that administration of the active compound is "immediately after the consumption of food" is met by the reference because (i) being in intimate mixture with the food, the sequences of administration possible thereby include the element of the claims, i.e., in a given portion of food wherein the compound and food are mixed, sequences of food then compound and compound then food are within the references teachings and the former meets the claim requirement; and (ii) multiple mouthfuls of the food/drug combination would include the instance where the compound, (with food), is administered and then, upon immediately taking the next mouthful, a food (with compound), step would occur, thus also meeting the requirement of the claims. While the reference does not explicitly highlight the above, it is believed that such eating sequences would have been once envisaged and thus in the possession of the public.

Finally, while the authors report rabbits as subjects, it is believed that humans would also be at once envisaged and placed in the possession of the public given the explicit teaching at page 206, col. 1, last line of the first, partial paragraph that "...our findings in rabbits may reasonably be extrapolated to predict the changes in plasma lipids in humans treated with this drug.". None of the present claims are directed to a specific patient/subject, however, humans

would be encompassed by the claimed hosts, and thus the above teaching by the authors is germane to the instant issue of anticipation.

Accordingly, the claims are deemed anticipated and therefore properly rejected.

II Claims 1-6, 10, 16-21, 25-30 and 34-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Gumkowski et al., (U.S. Patent Application Publication No. 2006/0014788; cited by the Examiner).

Gumkowski et al. teach pharmaceutical compositions comprising a CETP inhibitor, including the claimed compound, i.e., "Compound B", (see page 48, col. 1), as well as various co-solvents, surfactants and, optionally a digestible oil, (page 5, cols. 1-2, paragraphs [0048] – [0098]. The composition may be presented in various forms, such as solutions, suspensions, emulsions or as fill in encapsulated dosage forms such as hard or soft gelatin capsules (page 2, paragraph [0018]). The amount of the compound which may be in the composition is taught to range from 5 to 500 mg, (page 6, middle of paragraph [0112]; compare to present claims 2 and 3, for example, where dosage ranges of from "about" 100 mg to 1800 mg or from 300 mg to 900 mg are required). Gumkowski et al. further teach that the compositions, e.g., the pre-concentrates used to fill the capsules, may be added to sodas or food such as ice cream (page 6, col. 2, last sentence of paragraph [0112].

Gumkowski et al. further teach that the administration of such above compositions can be useful for the raising of HDL cholesterol, lowering LDL cholesterol and treating atherosclerosis, i.e., they teach that one of the problems they solved was "for a well-tolerated agent that can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis" (sentence bridging cols. 1-2 on page 1). Further, it is taught that their invention

"relates to encapsulated formulations of [CETP] inhibitors, (see present claim 25), for use in mammals, especially humans, which for mutations provide increased concentrations of CETP inhibitors for absorption, *hence higher bioavailability*.", (page 1, paragraph [0001], emphasis added; compare to present claim 1, for example, which recites "A method for increasing bioavailability...".

The requirement in claims 6, 21, 30 and 40, the requirement therein that administration of the active compound is "immediately after the consumption of food" is met by the reference because such would occur after the first intake of the food products highlighted by in the reference and before the last intake of such food products. Also, the dosages of the reference as well as the timing of administration with respect to food, which is, at the very least, simultaneously with the soda or ice cream, are within the claimed ranges and thus meet the requirements where set forth.

Finally, the requirement in present claim 16 for "increasing the extent of absorption" is met by the reference because (i) such would have inherently occurred given that the same composition containing the same drug is present in the instant claims and the reference and the administration of such would place the compound in the same environment in both the present claims and in the reference; and/or (ii) in the abstract at line 1, for example, the reference teaches the concept of "improved solubility and bioavailability" and at paragraph [0001] teaches that the compositions disclosed therein provide "increased concentrations of CETP inhibitors for absorption, hence higher bioavailablity" which clearly would have placed the claimed concept of "increasing the extent of absorption" in the possession of the public.

III Claims 1-10 and 16-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Shinkai et al., (U.S. Patent No. 6,426,365; cited by Applicants, see the IDS filed April 12, 2004, cit. "AA").

Shinkai et al. teach pharmaceutical compositions comprising a CETP inhibitor, including the claimed compound, i.e., at Example 26, (see cols. 61-62), as well as various known pharmacologically acceptable carriers, sweeteners and flavor improving agents, which may be presented for oral or parenteral administration, including in the form of tablets (col. 30, lines 28-47, especially lines 34, 36, 40 and 47). Specific co-ingredients highlighted include lactose and carbohydrates such as starch (col. 30, line 45). The amount of the compound which may be in the composition is taught to range from, in an adult, 1 to 1000 mg and in particular 50 to 800 mg per day (col. 30, lines 60-62); compare to present claims 2 and 3, for example, where dosage ranges of from "about" 100 mg to 1800 mg or from 300 mg to 900 mg are required).

Respecting the biological activity of the compound, Shinkai et al. teach CETP inhibitory activity at, for example, the abstract at line 1 and col. 120, lines 65-66 and Tables 38-48. Further, the patentees teach that the compound is effective for the treatment of atherosclerosis or hyperlipidemia because of the activity of the compound to increase HDL and also decreasing levels of LDL (col. 4, lines 21-27).

While the patentees do not expressly teach that the compound is administered with food, such nevertheless is taught because both lactose and starch are foods, (i.e., see the Webster's Dictionary reference cited by the Examiner at page 494, col. 2, which teaches that "food" is "material, usually of plant or animal origin, containing or consisting of essential body nutrients, as *carbohydrates,* fats, proteins, vitamins *or* minerals, taken in and assimilated by an organism to

maintain growth and life", while Shinkai et al., as noted above, expressly identifies starch as carbohydrate, and, as shown in the Handbook of Pharmaceutical Excipients, ("the Handbook"), cited by the Examiner, lactose was known not only as a tablet or capsule diluent (page 153, col. 1, paragraph 2), but also, from the chemical structure at paragraph 6 on page 153, a carbohydrate. Additionally, the Handbook shows that starch is "an edible food substance" (page 293, col. 1, paragraph 14).

Also, the patentees do not report the pharmacokinetic results after such administration, however, the claimed pharmacokinetic characteristics and actions (see, e.g., present claims 1 and 16), such would have been inherent to the prior art method which otherwise meets the presently claimed requirements for the drug, amounts, the host and the physiological environment in which the administered drug would exist.

Respecting claims 6, 21, 30 and 40, the requirement therein that administration of the active compound is "immediately after the consumption of food" is met by the reference because being in intimate mixture with the food, the sequences of administration possible thereby include the element of the claims, i.e., in a given portion of food wherein the compound and food are mixed, sequences of food then compound and compound then food are within the references teachings and the former meets the claim requirement. While the reference does not explicitly highlight the above, it is believed that such administration sequence would have been once envisaged and thus in the possession of the public.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 10-21, 25-30, 34-40 and 44-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gumkowski et al., (U.S. Patent Application Publication No. 2006/0014788), for the reasons above applied to claims 1-6, 10, 16-21, 25-30 and 34-40, which reasons are here incorporated by reference, **or** claims 1-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shinkai et al., (U.S. Patent No. 6,426,365), for the reasons above applied to claims are 1-6, 10-21, 25-30, 34-40 and 44-50, which are here incorporated by reference, both in view of Remington's Pharmaceutical Sciences, ("Remington's").

The difference between the above and the claimed subject matter lies in that neither Gumkowski et al. nor Shinkai et al. disclose:

(i) providing the composition to patient in a container which is associated with prescribing information, i.e., an instruction means, or a kit which contains such container and such means; and

(ii) the full, exact range of active agents in Applicants' claims 2, 3, 17, 18, 26, 27, 36 and 37.

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i) in the pharmaceutical art, it was well recognized that in order to provide a given medicament to a patient, (i) such medicament would necessarily have to be packaged, i.e., put into a container, (see present claims 11-15 and 44-53; and Remington's at page 1723, under the heading "Packaging", e.g., "In filling a prescription, pharmacists may select a container from among various shapes, sizes, mouth openings, colors and composition...); and such package would necessarily be associated with a label on which was printed instructions for use, (see present claims 11-15 and 44-53; and Remington's beginning at page 1721, col. 2, under the heading "labeling", e.g., "The federal government has required that patient product information be provided with the dispensing of certain drugs to ensure that the patient is apprised of proper use of the medication, its benefits and risks, and signs of adverse reactions", (page 1723, col. 1, third paragraph). Further, with respect to labels and labeling, the distinction and description of these terms appears in The Federal Food, Drug and Cosmetic Act, (see Remington's at page 1855, col. 2, second full paragraph). Given the above, the artisan would have been motivated to package the medicament in a container and associate a label or labeling means with such container, thus meeting the physical requirements of present claims 11-15 and 44-53.

While neither Gumkowski et al. nor Shinkai et al. teach the subject matter which is

written on the labels as in present claims 11-15 and 44-53, such does not diminish the propriety of the present rejection. The specific printed information is not material covered under patent laws, but rather copyright laws. Also, even if such were covered under patent laws, the limitation in the claims relating to the subject matter of the information on the instruction means is seen as no more than a statement of intended use for the claimed composition and such a statement does not impart any physical limitation to the composition that is not found in, or made obvious by the prior art. Further, see MPEP § 2112.01(III), where it is set forth under the heading "Product Claims – Nonfunctional Printed Matter Does Not Distinguish Claimed Product From Otherwise Identical Prior Art Product":

> "'Where the only difference between a prior art product and a claimed product is printed matter that is not functionally related to the product, the content of the printed matter will not distinguish the claimed product from the prior art. *In re Ngai*, **>367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004)< (Claim at issue was a kit requiring instructions and a buffer agent. The Federal Circuit held that the claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.). See also *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983)('Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability .... [T]he critical question is whether there exists any new and unobvious functional relationship between the printed matter and the substrate.')", (emphasis added).

Here, there is no unobvious functional relationship between the printed matter and the substrate, e.g., the container. Accordingly, no patentable distinction can be found in this element of the claimed subject matter.

(ii) Both references teach dosage ranges with either overlap or encompass the presently claimed dosage requirements. "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)", (see MPEP 2144.05(II)). The determination of the optimum dosage regimen to employ with the presently claimed active agents would have been a matter well within the purview of one of ordinary skill in the art and such determination would have been made in accordance with a variety of factors. These would have included the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, the dosage regimen that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed, specific dosage amounts are not seen to be inconsistent the dosages that would have been determined by the skilled artisan.

Accordingly, the claims are deemed properly rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

I Claims 1-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 6,426,365 (Shinkai et al., cited by Applicants, see the IDS filed April 12, 2004, cit. "AA"), claims 1-17 of U.S. Patent No. 6,753,346, (Shinkai et al., cited by Applicants, see IDS filed October 13, 2004, Doc. No. "BT"), ***or*** **provisionally rejected** on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent Application No. 10/825,531, (Attorney Docket listed as 06501-036002 and which has an assignee common to the present application, i.e., Japan Tobacco).

Although the conflicting claims are not identical, they are not patentably distinct from each other because in practicing the instantly claimed methods of increasing bioavailability; increasing the extent of absorption; decreasing the activity of CETP; treating a cardiovascular disease, or a kit comprising the presently claimed compound, a container and a labeling means, one would necessarily have to be practicing the claimed subject matter of the '365 or '346 patent or the '531 application because the '346 or '365 patent or '531 application claims are directed to

the same compound as utilized in the presently claimed subject matter, e.g., see claim 5 of the '531 application, page 123 of the application, third compound from the bottom; claims 1-7 of the '346 patent, and claim 5 of the '365 patent, col. 133, lines 10-11.

Also, while the present claims include elements not highlighted in the '365 or '346 patent or '531 application, the present claims recite "comprising" and thus do not patentably exclude such other elements.

Additionally, for the reasons above, the method of claims 8-17 of the '346 patent or the '531 application, claims 16-18, are directed to the same, ultimate objectives as in present claims 25, (decreasing CETP activity) and 34-35, (treating hyperlipidemia or atherosclerosis), i.e., the mechanisms recited in the claims of the '346 patent do not represent a patentably distinct method because ultimately, the claim would be useful for the treatment of hyperlipidemia or atherosclerosis.

It should be noted that in the above one-way obviousness analysis, the present claims are viewed as being the basis upon which the claims of the '365 or '346 patents or the '531 application could be rejected. Therefore, it is immaterial that the co-pending claims do not include all of the method objectives and steps as in the present claims. What is ultimately germane is that one could not practice the presently claimed subject matter without also practicing the subject matter of the '365 or '346 patents or '531 application.

Accordingly, for the above reasons, the claims are deemed properly rejected.

II Claims 1-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 11-23 of co-pending Application No. 10/802,220 ***or*** claims 1-5, 7-32, 34-52, 54-83 of co-pending Application No. 10/835,916.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending applications make use of the same compound which is in the present claims, e.g., see claim 1 of the '916 application or claim 11 of the '220 application and therefore in practicing the methods, compositions and/or kits of the co-pending applications, one would necessarily be practicing the methods and kits of the present claims. Insofar as the same compound is involved and would be present in the same physiological environment and would be present with food, (see the '220 application at claims 18-23 and the '916 application at claim 83, the results not reported in the claims would be inherently present.

Additionally, as above, it should be noted that in the above one-way obviousness analysis, the claims of the '916 or '220 application are viewed as being the basis upon which the claims of the present application could be rejected. Therefore, it is immaterial that the co-pending or present claims do not include all of the method objectives and steps as in the present claims. For example, claim 1 of the '916 application requires the presence of an HMG-CoA reductase inhibitor, while the present claims are silent in this respect. However, the present claims recite comprising, and thus do not patentable exclude an HMG-CoA reductase inhibitor from being present. What is ultimately germane is that one could not practice the presently claimed subject matter without also practicing the subject matter of the '220 or '916 application.

Also, respecting the kit claims of the '916 application and the kit claims of the present application, it is noted that the written subject matter on the instruction means is different. However, it is only important that the container is in physical relationship with such means in both sets of the claims. The subject matter of the written material is not germane to the instant

analysis, (see above under the rejection based on 35 U.S.C. §103 for a more detailed explanation, which is here incorporated by reference).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Accordingly, for the above reasons, the claims are deemed to be properly objected to/rejected and none are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1614

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